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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/019,651	07/08/2002	Elisabeth Csoregi	50159-026	5727
20277	7590	01/05/2004	EXAMINER	
MCDERMOTT WILL & EMERY 600 13TH STREET, N.W. WASHINGTON, DC 20005-3096			WEBER, JON P	
			ART UNIT	PAPER NUMBER
			1651	
DATE MAILED: 01/05/2004				

Please find below and/or attached an Office communication concerning this application or proceeding.

Advisory Action

Application No.

10/019,651

Applicant(s)

CSOREGI ET AL.

Examiner

Jon P Weber, Ph.D.

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--The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

THE REPLY FILED 24 November 2003 FAILS TO PLACE THIS APPLICATION IN CONDITION FOR ALLOWANCE. Therefore, further action by the applicant is required to avoid abandonment of this application. A proper reply to a final rejection under 37 CFR 1.113 may only be either: (1) a timely filed amendment which places the application in condition for allowance; (2) a timely filed Notice of Appeal (with appeal fee); or (3) a timely filed Request for Continued Examination (RCE) in compliance with 37 CFR 1.114.

PERIOD FOR REPLY [check either a) or b)]

- a) ☒ The period for reply expires 4 months from the mailing date of the final rejection.
b) ☐ The period for reply expires on: (1) the mailing date of this Advisory Action, or (2) the date set forth in the final rejection, whichever is later. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of the final rejection. ONLY CHECK THIS BOX WHEN THE FIRST REPLY WAS FILED WITHIN TWO MONTHS OF THE FINAL REJECTION. See MPEP 706.07(f).

Extensions of time may be obtained under 37 CFR 1.136(a). The date on which the petition under 37 CFR 1.136(a) and the appropriate extension fee have been filed is the date for purposes of determining the period of extension and the corresponding amount of the fee. The appropriate extension fee under 37 CFR 1.17(a) is calculated from: (1) the expiration date of the shortened statutory period for reply originally set in the final Office action; or (2) as set forth in (b) above, if checked. Any reply received by the Office later than three months after the mailing date of the final rejection, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

1. ☐ A Notice of Appeal was filed on _____. Appellant's Brief must be filed within the period set forth in 37 CFR 1.192(a), or any extension thereof (37 CFR 1.191(d)), to avoid dismissal of the appeal.
2. ☐ The proposed amendment(s) will not be entered because:
(a) ☐ they raise new issues that would require further consideration and/or search (see NOTE below);
(b) ☐ they raise the issue of new matter (see Note below);
(c) ☐ they are not deemed to place the application in better form for appeal by materially reducing or simplifying the issues for appeal; and/or
(d) ☐ they present additional claims without canceling a corresponding number of finally rejected claims.

NOTE: _____.

3. ☐ Applicant's reply has overcome the following rejection(s): _____.
4. ☐ Newly proposed or amended claim(s) _____ would be allowable if submitted in a separate, timely filed amendment canceling the non-allowable claim(s).
5. ☒ The a) ☐ affidavit, b) ☐ exhibit, or c) ☒ request for reconsideration has been considered but does NOT place the application in condition for allowance because: See attachment.
6. ☐ The affidavit or exhibit will NOT be considered because it is not directed SOLELY to issues which were newly raised by the Examiner in the final rejection.
7. ☒ For purposes of Appeal, the proposed amendment(s) a) ☐ will not be entered or b) ☒ will be entered and an explanation of how the new or amended claims would be rejected is provided below or appended.

The status of the claim(s) is (or will be) as follows:

Claim(s) allowed: _____.

Claim(s) objected to: 22.

Claim(s) rejected: 13-21.

Claim(s) withdrawn from consideration: _____.

8. ☐ The drawing correction filed on _____ is a) ☐ approved or b) ☐ disapproved by the Examiner.
9. ☐ Note the attached Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____.
10. ☐ Other: _____

Jon P Weber, Ph.D.
Primary Examiner
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Status of the Claims

The response with amendments After Final filed 24 November 2003 has been received and entered. Claims 13-22 have been presented for examination.

Claim Rejections - 35 USC § 112

Claims 20-21 stand rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The amendments to these claims have been entered despite their confusing nature, because there is no provision to enter amendments in part, and the other amendments to the claims and specification place this application in better condition for allowance or appeal.

The amended claims are still very confusing. The following language is suggested.

20. A method for the detection or determination of freshness biomarkers or of the content of freshness biomarkers in a food sample, comprising the steps of establishing a standard curve between the electrical output of the biosensor of claim 13 and freshness, wherein said freshness biomarkers are biogenic amines, applying said sample to the biosensor of claim 13, detecting an electrical output from said biosensor, and comparing the electrical output of the biosensor when applied to the sample with said standard curve for freshness biomarkers to detect and determine the freshness of the food sample.

21. A method for the detection or determination of histamine in a body fluid sample, in medical diagnoses or in the treatment of a disease, comprising the steps of establishing a standard curve between the electrical output of the biosensor of claim 13 and histamine, applying

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said sample to the biosensor of claim 13, detecting an electrical output from said biosensor, and comparing the electrical output of the biosensor when applied to the sample with said standard curve for histamines to detect and determine the histamines of the sample.

Claim Rejections - 35 USC § 103

Claims 13-19 and 21 stand rejected under 35 U.S.C. 103(a) as being unpatentable over Heller et al. (WO 199323748) in view of Ohashi et al. (US 5,565,329).

It is argued that the Expasy reference does not disclose topaquinone as AO cofactor. The Brenda/Cogoni reference was said not to be present. It is argued that AO and peroxidase are isolated from each other in Heller and not coupled as instantly claimed. It is urged that Ohashi does not remedy this deficiency. It is also argued that the grass pea AO has improved sensitivity compared to other AOs. It is urged that no cogent scientific reasoning was presented why there is no advantage to selection of one AO over another. A data table is presented alleged unexpected advantages of grass pea AO over *Aspergillus niger* AO.

The Expasy reference clearly discloses topaquinone as cofactor in the middle of the page under "Cofactors" as well as copper.

It is not known why the Brenda/Cogoni reference was not sent to applicants inasmuch as the rest of the references were sent. A copy of this reference is attached to this action. Nevertheless, the internet URL for this citation was provided in the Office action and applicants could have availed themselves thereof. This reference was provided to establish that other AOs (*Phaseolus vulgaris* and *Lathyrus cicera*) were known in the art and contain copper as a cofactor.

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Coupling of the enzymes for reaction purposes does not require their direct covalent conjugation, just that the reactions be coupled chemically. This does not even appear to be contemplated by the instant application. In the instant application, the enzymes are not mixed together either, but are layered sequentially on top of each other on the electrode surface (with drying of the layers between applications). In a sense, then, since the instant enzymes are in separate layers, they are not physically coupled instantly either, just chemically. Chemical coupling requires only that the product of the first enzyme in the couple is freely diffusible to the second enzyme for reaction. This can be accomplished by a mixture of the two enzymes in a homo- or heterogeneous solution, or covalently conjugating the two enzymes, or by placing the enzymes in such close physical proximity that diffusion of reactants can occur between the two enzymes. These are matters well known in the art of chemistry and biochemistry. Numerous examples of coupled reactions can be found in *Methods of Enzymology*. One example is the coupling of any glutamate producing reaction to glutamate dehydrogenase, where detection of changes in [NADH] can be readily detected spectrophotometrically or electrochemically.

There are a myriad of known AOs. Two of these enzymes have allegedly been compared in the Table in the response. First, the data in this table should be properly submitted in Declaration form inasmuch as this data is not part of the disclosure. Second, it is not clear that the showing is a fair side-by-side comparison. The electrodes are different. The method of forming the electrodes is different. The amounts of each enzyme are not given (see Table 1 of Niculescu). The purity of the enzymes is not disclosed. Overall, the lack of information makes the use of this information questionable. Finally, it is not clear that *Aspergillus niger* AO is necessarily representative of all other AOs. As pointed out in Niculescu, AO is widely

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distributed in microorganisms, mammals and plants. That Ohashi used enzyme from this source does not mean that it is the only possible alternative source to which comparison should be made.

Applicant's arguments filed 24 November 2003 have been fully considered but they are not persuasive. The rejection under 35 U.S.C. 103 is adhered to for the reasons of record and the additional reasons above.

Allowable Subject Matter

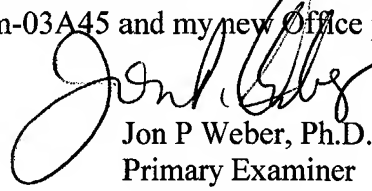
Claim 22 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon P Weber, Ph.D. whose telephone number is 703-308-4015. The examiner can normally be reached on daily, off 1st Fri, 9/5/4.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael G. Wityshyn can be reached on 703-308-4743. The fax phone number for the organization where this application or proceeding is assigned is (703) 872-9306.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-0196.

My new Office room number will be Rem-03A45 and my new Office phone number will be 571-272-0925 after 15 January 2004.



Jon P Weber, Ph.D.
Primary Examiner
Art Unit 1651

JPW
24 December 2003